REMARKS

Claims 1-7, 9-12, 14 and 15 are pending in the application. .

Reconsideration of the application is respectfully requested in view of the following remarks. For the Examiner's convenience, Applicant's remarks are presented in the order in which they were raised in the Office Action.

A. Claim Rejections Under 35 U.S.C. § 102

Claims 1-7, 9, 11 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by an Asmar et al. abstract from the sixteenth meeting of the American Society of Hypertension (2001). The Examiner cites Asmar for disclosing the administration of telmisartan to diabetes type 2 patients with essential hypertension. Asmar is also cited for teaching a 40 mg per patient dosage. The Examiner states that telmisartan administered to type 2 diabetes patients with hypertension "inherently treats metabolic syndrome since hypertension is a symptom associated with hypertension." (Office Action, page 3).

Applicants respectfully traverse. "Under the principles of inherency, if the prior art **necessarily** functions in accordance with, or includes, the claims limitations, it anticipates." (emphasis added; *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002); quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)). "In general, a limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, at 1379 (Fed. Cir. 2003; citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)).

Recently, the Federal Circuit confirmed that under 35 U.S.C. § 101 "[n]ew uses of old products or processes are indeed patentable subject matter." (*Perricone v. Medicis Pharm. Corp.*, Case Nos. 05-1022, -1023; 432 F.3d 1368, 2005 U.S. App. LEXIS 28061, at *24 (Fed. Cir., Dec. 20, 2005)). The Federal Circuit reiterated that a patent to an apparatus does not necessarily prevent a subsequent inventor from obtaining a patent on a new method of using the apparatus. (*Id.*; citing

Catalina Marketing International, Inc. v. Cool Savings.com, Inc. 289 F.3d 801, 809 (Fed. Cir. 2002)) [1]

Applicants submit that the Examiner's conclusion that treatment with telmisartan of type 2 diabetes patients with hypertension inherently anticipates treatment of diabetes type 2 patients with metabolic syndrome is incorrect because all patients with hypertension and diabetes do not have the metabolic syndrome. Epidemiologic studies have shown that close to one million Americans have diabetes and hypertension without having the metabolic syndrome (Alexander C.M. *et al.* Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). *Diabetes*. 2003 May; 52(5):1210-1214; *see* Table 1.; copy submitted herewith).

"Metabolic syndrome" is defined by the National Cholesterol Education Program as requiring the presence of any three of the following five risk factors: increased waist circumference, increased triglycerides, decreased HDL cholesterol, increased blood pressure, and increased fasting serum glucose. (*see* Table 2 in Grundy SM, *et al.*, Diagnosis and Management of the Metabolic Syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005 Oct 25; 112(17):2735-2752; copy submitted herewith). Therefore, it follows that one suffering from metabolic syndrome does not necessarily suffer from hypertension or diabetes. Patients with diabetes and hypertension have increased blood sugar and increased blood pressure but do not necessarily have two more of the additional risk factors required to meet the definition of the metabolic syndrome according to the American Heart Association and National Heart, Lung, and Blood Institute's National Cholesterol Education Program (or any of the other

[1] The *Perricone* court dismissed an inherency conclusion of the District Court because the cited prior art (Pereira) disclosure of topical application to a skin surface could not render inherent a topical application to skin sunburn. "The issue is not, as the dissent and district court imply, whether Pereira's lotion if applied to skin sunburn would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not." *Id.*

criteria for defining the metabolic syndrome set forth since 1998 by several different organizations; *see* Grundy, Table 1).

Conversely, it is noted that many patients with the metabolic syndrome do not have hypertension or diabetes. For example, someone with an increased waist circumference, increased triglycerides, and low HDL cholesterol level would have the metabolic syndrome even in the absence of hypertension or diabetes. Nearly 14% of patients over the age of 50 years (about 76.1 million Americans) with metabolic syndrome do not have diabetes or hypertension (*see* Alexander, Table 2)

Since the conditions of diabetes and hypertension do not necessarily correlate with the presence of the metabolic syndrome, Applicants submit that Asmar's teaching of administering telmisartan to patients with diabetes and hypertension does not necessarily teach the administration of telmisartan to patients with the metabolic syndrome. Therefore, Asmar does not inherently anticipate claims 1-7, 9, 11 and 12 and Applicants respectfully request withdrawal of this ground of rejection for the claims.

B. Claim Rejections Under 35 U.S.C. § 103

Claims 10, 14 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Asmar et al. The Examiner states that the topical administration of telmisartan or a total daily effective oral dose is obvious over the alleged inherent anticipation of administration of telmisartan to patients with metabolic syndrome by Asmar. Claims 10, 14 and 15 depend from claim 1.

As discussed in detail above under section (A), Asmar does not inherently teach or suggest the administration of telmisartan to patients with metabolic syndrome. Therefore, Applicants respectfully request withdrawal of the rejection of claims 10, 14 and 15 for obviousness over Asmar.

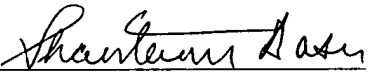
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and allow this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 421842000400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 31, 2006

Respectfully submitted,

By 

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NCEP-Defined Metabolic Syndrome, Diabetes, and Prevalence of Coronary Heart Disease Among NHANES III Participants Age 50 Years and Older

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Although the individual components of the metabolic syndrome are clearly associated with increased risk for coronary heart disease (CHD), we wanted to quantify the increased prevalence of CHD among people with metabolic syndrome. The Third National Health and Nutrition Examination Survey (NHANES III) was used to categorize adults over 50 years of age by presence of metabolic syndrome (National Cholesterol Education Program [NCEP] definition) with or without diabetes. Demographic and risk factor information was determined for each group, as well as the proportion of each group meeting specific criteria for metabolic syndrome. The prevalence of CHD for each group was then determined. Metabolic syndrome is very common, with ~44% of the U.S. population over 50 years of age meeting the NCEP criteria. In contrast, diabetes without metabolic syndrome is uncommon (13% of those with diabetes). Older Americans over 50 years of age without metabolic syndrome regardless of diabetes status had the lowest CHD prevalence (8.7% without diabetes, 7.5% with diabetes). Compared with those with metabolic syndrome, people with diabetes without metabolic syndrome did not have an increase in CHD prevalence. Those with metabolic syndrome without diabetes had higher CHD prevalence (13.9%), and those with both metabolic syndrome and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither. Metabolic syndrome was a significant univariate predictor of prevalent CHD (OR 2.07, 95% CI 1.66–2.59). However, blood pressure, HDL cholesterol, and diabetes, but not presence of metabolic syndrome, were significant multivariate predictors of prevalent CHD. The prevalence of CHD markedly increased with the presence of metabolic syndrome. Among people with diabetes, the prevalence of metabolic syndrome was very high, and those with diabetes and metabolic syndrome had the highest prevalence of CHD. Among all individuals with diabetes, prevalence of CHD was increased compared with those with metabolic syndrome without diabetes. However, individuals with diabetes without metabolic syndrome had no greater prevalence of CHD compared with those with neither. *Diabetes* 52:1210–1214, 2003

The frequent simultaneous presence of obesity, hyperlipidemia, diabetes, and hypertension was first described in the late 1960s (1). This association (i.e., diabetes, hypertension, and obesity with hyperlipidemia) was subsequently highlighted in the late 1970s by a number of German researchers, including Haller and colleagues (2,3). They coined the term "metabolic syndrome" and described its association with atherosclerosis. In 1991, Ferrannini et al. (4) described the same clustering of abnormalities in this cardiovascular and metabolic syndrome as being caused by insulin resistance and concluded that "insulin resistance syndrome" was the appropriate name for this condition. At about the same time, Reaven (5,6) agreed that insulin resistance was the cause of these abnormalities. He initially did not include abdominal obesity, however, and he used the term "syndrome X." It appears that metabolic syndrome, insulin resistance syndrome, and syndrome X all refer to the same clustering of risk factors associated with atherosclerosis and coronary heart disease (CHD). In fact, Meigs et al. (7) found that among nondiabetic subjects from the Framingham Offspring Study, a clustering of risk factors, including hyperinsulinemia, dyslipidemia, hypertension, and glucose intolerance (rather than hyperinsulinemia alone), characterized the underlying features of the insulin resistance syndrome.

The pathophysiology of this syndrome remains a subject of continuing controversy, although some have suggested a causal relationship with insulin resistance and/or visceral adiposity. At the same time, it has become increasingly apparent that even small increases in fasting or postprandial glucose values (including impaired glucose tolerance or impaired fasting glucose) impart an increased risk for cardiovascular morbidity and mortality (8–14). In the Quebec Prospective Study, Lamarche et al. (15) showed that even without hyperglycemia, elevated levels of insulin (i.e., insulin resistance), small dense LDL cholesterol, and apolipoprotein B were associated with risk for ischemic heart disease.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provided a definition for metabolic syndrome (16). The NCEP criteria are practical for physicians to use, since the variables defining

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ATP, Adult Treatment Panel; CHD, coronary heart disease; NCEP, National Cholesterol Education Program; NCHS, National Center for Health Statistics; NHANES III, Third National Health and Nutrition Examination Survey.

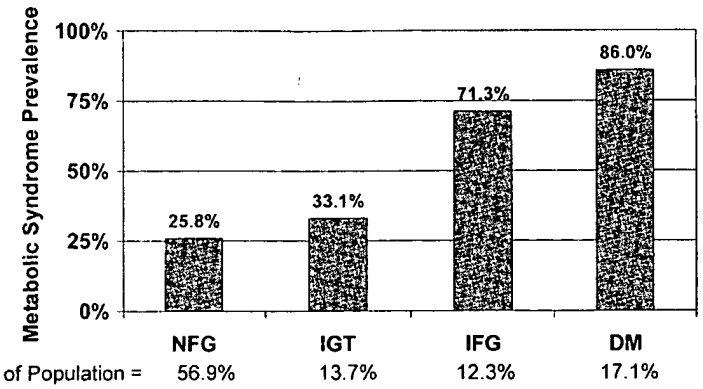

FIG. 1. Age-adjusted prevalence of metabolic syndrome in the U.S. population over 50 years of age categorized by glucose intolerance (NFG, normal fasting glucose; IGT, impaired glucose tolerance without impaired fasting glucose; IFG, impaired fasting glucose with or without impaired glucose tolerance; DM, diabetes mellitus).

metabolic syndrome are commonly available in clinical practice. Ford et al. (17) have previously shown that metabolic syndrome is common in people ≥50 years of age. Since glucose intolerance is an important part of metabolic syndrome and increases with age, this report will focus on the interactions among metabolic syndrome, hyperglycemia, and prevalence of CHD. We used Third National Health and Nutrition Examination Survey (NHANES III) data to evaluate the prevalence of CHD in individuals ≥50 years of age with metabolic syndrome, with and without diabetes, using the NCEP definition.

RESEARCH DESIGN AND METHODS

NHANES III was conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, in two phases: phase 1 (1988–1991) and phase 2 (1991–1994) (17–19). For this analysis, subjects surveyed during either phase are included. The survey was a stratified probability sample of the civilian, noninstitutionalized U.S. population. African Americans, Mexican Americans, and the elderly were oversampled to provide more accurate estimates of their characteristics within their respective populations and the population as a whole. Each respondent was assigned a weight based on geographic and demographic characteristics to allow the calculation of population-based estimates. A subset of adults ≥50 years of age representing 76.1 million Americans was used for this analysis.

An adult in-home questionnaire was administered to sampled subjects ≥17 years of age. Physical exams were conducted on those subjects who were ambulatory and who consented to the examination given at a date subsequent to the in-home interview. Adults ≥50 years of age who were scheduled for and received morning physical exams after a fast of at least 9 h were retained for analysis (n = 3,510). During NHANES III, oral glucose tolerance testing was conducted on approximately one-half of the examinees aged 40–74 years. This subsample most closely conformed to the World Health Organization criteria for oral glucose tolerance testing to identify diabetes and was the population used to estimate the prevalence of diabetes and impaired glucose tolerance.

The NCEP ATP III panel defined metabolic syndrome as the presence of three or more of the following risk determinants: *1*) increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); *2*) elevated triglycerides (≥150 mg/dl); *3*) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); *4*) hypertension (≥130/≥85 mmHg); and *5*) impaired fasting glucose (≥110 mg/dl) (16).

We determined the prevalence of metabolic syndrome based on fasting glucose levels and glucose tolerance and then stratified the population into four groups (no metabolic syndrome or diabetes, metabolic syndrome without diabetes, metabolic syndrome with diabetes, and no metabolic syndrome with diabetes) using the NCEP definition of the metabolic syndrome and either self-reported history of diabetes or a fasting plasma glucose value ≥7.0 mmol/l (≥126 mg/dl) (16,20). Serum lipoproteins were evaluated as part of the blood biochemistry panel of the laboratory exam. LDL cholesterol was calculated using the Friedewald equation for those with serum triglyceride levels ≤400 mg/dl (21). Blood pressure is reported as the average of six readings, three taken during the household interview and three taken during the physical exam. The NCEP metabolic syndrome cutpoint for blood pressure is ≥130/85 mm/Hg. Individuals reporting a history of hypertension and current blood pressure medication use were defined as having hypertension regardless of measured blood pressure values. BMI was calculated as the weight of the individual in kilograms divided by the square of the height in centimeters. Individuals with a history of diabetes or glycemic medication use were defined as having diabetes regardless of measured fasting glucose values. Insulin measurements were performed using the Pharmacia Diagnostics radioimmunoassay kit. Insulin sensitivity was calculated using the formula of McAuley et al. (22) as the exponent of [2.63 − 0.28 ln(insulin mU/l) − 0.31 ln(triglyceride mmol/l)] and the homeostasis model assessment of insulin resistance (23).

As a result of low prevalence of CHD in the population <50 years of age (3.1% for <50 years vs. 12.3% for ≥50 years, unadjusted rates) and since metabolic syndrome clusters with age, we chose to focus our analysis on those ≥50 years of age. Presence of CHD is defined as self-reported myocardial infarction or a positive response to the angina pectoris section of the Rose Questionnaire (24). Our definition of CHD was based upon information available in the NHANES III database, but probably represents an underestimate of the true prevalence. Defining CHD only as self-reported without including information from the Rose Questionnaire reduces the prevalence of CHD by 2–3% but does not otherwise change our results.

Statistical analysis. All data were analyzed using SAS version 8e and SAS-callable SUDAAN version 8.0.1 (25,26). SUDAAN uses characteristics of the sample design and sample weights to calculate appropriate estimates of variance. The CROSSTAB and DESCRIPT procedures of SUDAAN were used to produce frequencies of categorical variables and means ± SE of continuous variables. Overall tests of significance across the four study groups were evaluated by ANOVA using the MULTILOG and REGRESS procedures. Summary statistics are presented as means ± SE for continuous measures and frequency percentage for all discrete measures. Age-adjusted CHD prevalence rates were computed by the direct method using the age distribution of the U.S. population based on the 2000 U.S. Census.

For Fig. 2, tests of significance were calculated using pairwise comparisons adjusted for multiple comparisons by the method of Bonferroni. A multivariate logistic model predicting CHD was developed using the RLOGIST procedure in SUDAAN. The independent variables of interest, the individual risk factors of metabolic syndrome as defined by NCEP, diabetes, and an indicator variable for metabolic syndrome (a proxy for the interactions of the individual factors) were fit simultaneously. The odds ratios and 95% CIs for having CHD given the presence of any one risk factor, controlling for all others, are presented in Table 3.

The attributable risk of CHD was calculated as the difference in prevalence between the population without either diabetes or metabolic syndrome and the appropriate group (i.e., metabolic syndrome without diabetes, diabetes without metabolic syndrome, diabetes and metabolic syndrome) divided by the prevalence of CHD in the appropriate group.

RESULTS

Age-adjusted prevalence of metabolic syndrome in the U.S. population ≥50 years of age categorized by glucose intolerance is shown in Fig. 1. There is a stepwise increase in prevalence of metabolic syndrome with worsening glucose tolerance from 26% in those with normal fasting glucose rising to 86% in those with diabetes. As can be seen in Table 1, metabolic syndrome is very common in the U.S. population over the age of 50 years, with ~43.5% meeting the NCEP criteria. In contrast, diabetes without metabolic syndrome is uncommon in the over-50 population (only ~13% of diabetic patients do not meet criteria for metabolic syndrome).

For most cardiovascular risk factors, the group with

TABLE 1
Demographic and laboratory characteristics among U.S. population ≥50 years

	No diabetes		Diabetes			
	No metabolic syndrome	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome	*P**	Total
Percentage of population	54.2%	28.7%	2.3%	14.8%		
Factor						
% Male	45.5	42.2	55.7	48.2	0.1218	45.2
Age (years)	63.4 ± 0.4	65.2 ± 0.6	68.5 ± 0.8	65.5 ± 0.6	<0.0001	64.3 ± 0.3
% Smoker	22.3	19.0	24.9	16.1	0.2757	20.5
LDL cholesterol (mg/dl)	138.3 ± 1.4	143.9 ± 1.7	135.3 ± 3.5	138.8 ± 2.2	0.0322	139.9 ± 1.1
HDL cholesterol (mg/dl)	56.5 ± 0.6	44.0 ± 0.7	58.8 ± 2.2	42.4 ± 1.1	<0.0001	50.9 ± 0.5
Triglycerides (mg/dl)	119.9 ± 2.5	211.9 ± 5.4	118.0 ± 6.3	231.5 ± 9.0	<0.0001	162.6 ± 3.3
Systolic BP mm/Hg	129.1 ± 0.8	140.3 ± 0.7	129.7 ± 3.0	139.7 ± 1.1	<0.0001	133.9 ± 0.6
Diastolic BP mm/Hg	73.9 ± 0.3	78.3 ± 0.6	72.3 ± 1.2	75.0 ± 0.6	<0.0001	75.3 ± 0.3
BMI	25.4 ± 0.2	29.6 ± 0.3	24.7 ± 0.8	30.9 ± 0.4	<0.0001	27.4 ± 0.2
Insulin sensitivity	7.4 ± 0.1	5.5 ± 0.1	6.7 ± 0.2	4.9 ± 0.1	<0.0001	6.5 ± 0.1
HOMA-IR	2.1 ± 0.1	3.6 ± 0.1	10.0 ± 3.0	11.5 ± 0.9	<0.0001	4.1 ± 0.2

Data are means ± SE unless otherwise indicated. *Statistical significance of differences across the groups (ANOVA). BP, blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance.

metabolic syndrome and without diabetes was more comparable to the diabetes with metabolic syndrome group than to both groups without metabolic syndrome. An exception to this observation was HbA_{1c} levels, where the two diabetes groups were comparable. The two groups without metabolic syndrome were also very similar regardless of absence or presence of diabetes. Insulin resistance was highest and insulin sensitivity was lowest in the diabetes with metabolic syndrome group (4.9 ± 0.1), followed by the metabolic syndrome without diabetes group (5.5 ± 0.1). Insulin resistance was lowest and insulin sensitivity was highest in the group without metabolic syndrome or diabetes (7.4 ± 0.1, $P < 0.0001$).

The proportion of each group meeting each NCEP criterion for metabolic syndrome is shown in Table 2. Again, the characteristics of the two metabolic syndrome groups are comparable with the exception of fasting glucose (by definition) and are different from the two groups without metabolic syndrome.

Figure 2 shows the age-adjusted prevalence of CHD in the various groups. The overall prevalence in this age group was 11.7%. Americans over 50 years of age without metabolic syndrome and diabetes had the lowest CHD prevalence (8.7%), and those with both metabolic syndrome and diabetes had the highest (19.2%). Individuals with diabetes in the absence of metabolic syndrome did not have an incremental increase in CHD prevalence compared with individuals with neither (7.5 vs. 8.7%, respectively). Differences between the groups, both overall and using pairwise comparisons, were all statistically significant ($P < 0.001$).

Not surprisingly, metabolic syndrome was a significant predictor of prevalent CHD in univariate analysis (OR 2.07, 95% CI 1.66–2.59). However, as shown in Table 3, blood pressure, HDL cholesterol, and diabetes, but not presence of metabolic syndrome, were significant predictors of prevalent CHD in multivariate analyses.

As shown in Table 4, the excess prevalence of CHD attributable to metabolic syndrome and/or diabetes was 37.4% (1.1 million cases of CHD) in the group with metabolic syndrome without diabetes and 50.3% (1.1 million cases of CHD) in the group with both metabolic syndrome and diabetes. The entire excess prevalence of CHD among those with diabetes was in the group with both diabetes and metabolic syndrome.

DISCUSSION

This analysis examined CHD prevalence by metabolic syndrome criteria from the NCEP and diabetes status based on 1997 American Diabetes Association criteria using NHANES III, the most recent large clinical survey of a representative sample of the U.S. population, which collected all necessary information to characterize individ-

TABLE 2
Criteria for metabolic syndrome among U.S. population ≥50 years

	No diabetes		Diabetes		
	No metabolic syndrome	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome	Total
Percentage of population	54.2%	28.7%	2.3%	14.8%	
Criterion					
% Waist circumference (M >102 cm; F >88 cm)	34.4	82.0	18.5	86.0	55.0
% Triglycerides ≥150 mg/dl	18.0	77.8	5.1	72.1	42.8
% HDL cholesterol (M <40 mg/dl; F <50 mg/dl)	16.5	70.7	2.6	69.7	39.5
Blood pressure ≥130/85 mm/Hg (%)	45.3	86.2	43.0	82.7	62.5
Fasting glucose >110 (%)	6.2	30.9	83.0	90.2	27.2

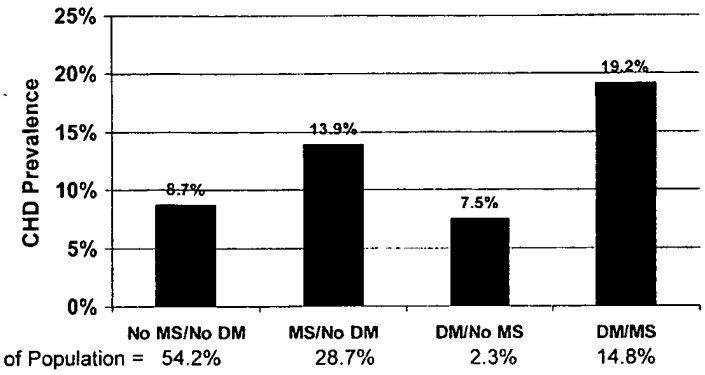

FIG. 2. Age-adjusted prevalence of CHD in the U.S. population over 50 years of age categorized by presence of metabolic syndrome and diabetes. Combinations of metabolic syndrome (MS) and diabetes mellitus (DM) status are shown.

uals by metabolic status. The prevalence of metabolic syndrome increases with increasing glucose intolerance. The prevalence of CHD markedly increases with the presence of metabolic syndrome. The prevalence of CHD among all participants with diabetes was increased compared with the prevalence among those with metabolic syndrome without diabetes. However, individuals with diabetes without metabolic syndrome had about the same prevalence of CHD as those with neither.

One possible reason for the excess prevalence of CHD associated with metabolic syndrome is the direct effect of insulin resistance on the heart and arteries (27). It is more likely that the bulk of the increased prevalence is mediated by known cardiovascular risk factors. Indeed, all five metabolic syndrome criteria are established cardiovascular risk factors. We know that the presence of multiple risk factors confers increased risk (28). However, it is unclear whether the metabolic syndrome confers elevated risk beyond the sum of its parts (29). Our multivariate analysis would suggest that the risk from metabolic syndrome is derived from its individual components, especially HDL cholesterol and blood pressure. However, modeling metabolic syndrome as the sole predictor of CHD yields more than a twofold increased risk compared with not having metabolic syndrome and is a convenient way to encapsulate a number of proven risk factors.

It has been argued that the excess prevalence of CHD seen in those with diabetes is directly associated with hyperglycemia. In our study, metabolic syndrome has been demonstrated to be much more important, with no increase in prevalence of CHD seen in people with diabetes in the absence of metabolic syndrome. Although one of the components of metabolic syndrome is fasting hyperglycemia and many of the subjects in this study with metabolic syndrome without diabetes still may have had hyperglycemia in the nondiabetic range, modestly increased glucose alone is unlikely to account for the increased CHD risk. Because *1*) most people with diabetes have type 2 diabetes and metabolic syndrome and *2*) most individuals with impaired fasting glucose also have metabolic syndrome, our work is consistent with our previous study using NHANES III data that showed an increased CHD prevalence in those with diabetes and impaired fasting glucose (30).

There are limitations to this analysis. Since the case fatality rate among people with diabetes is higher than in those without diabetes, this cross-sectional study is subject to survival bias, which would underestimate the impact of diabetes on CHD. The same may also be true for metabolic syndrome in the absence of diabetes. The NCEP criteria for metabolic syndrome have face validity, but have not yet been formally validated or studied. Since NHANES III was a cross-sectional study, we cannot infer causality from these associations. These results should be considered hypothesis-generating, which requires prospective studies among those with diabetes to demonstrate if those without the metabolic syndrome indeed have a lower cardiovascular risk than those with the syndrome. More recent studies have shown that there is a continuing epidemic of diabetes and obesity and suggest that NHANES III data, even adjusted for recent census data, may be underestimating the prevalence of diabetes and metabolic syndrome (31).

The prevalence of CHD markedly increases with presence of metabolic syndrome. Among people with diabetes, prevalence of metabolic syndrome was very high, and those with diabetes and metabolic syndrome had the highest prevalence of CHD. Among all individuals with diabetes, prevalence of CHD was increased compared to those with metabolic syndrome without diabetes. How-

TABLE 3
Prediction of CHD prevalence using multivariate logistic regression

Variable*	Odds ratio	Lower 95% limit	Upper 95% limit
Waist circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
HDL cholesterol*	1.74	1.18	2.58
Blood pressure*	1.87	1.37	2.56
Impaired fasting glucose	0.96	0.60	1.54
Diabetes*	1.55	1.07	2.25
Metabolic syndrome	0.94	0.54	1.68

*Significant predictors of prevalent CHD.

TABLE 4
Attributable risk of metabolic syndrome and diabetes for CHD in U.S. population ≥50 years

	No diabetes	Diabetes	
	Metabolic syndrome	No metabolic syndrome	Metabolic syndrome
Total population	21,841,000	1,750,000	11,263,000
Population with CHD	3,036,000	131,000	2,162,496
Attributable risk	37.4%	NM	54.7%

NM, not meaningful.

ever, individuals with diabetes without metabolic syndrome had no greater prevalence of CHD compared with those with neither.

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AHA/NHLBI Scientific Statement

Diagnosis and Management of the Metabolic Syndrome

An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement

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The metabolic syndrome has received increased attention in the past few years. This statement from the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) is intended to provide up-to-date guidance for professionals on the diagnosis and management of the metabolic syndrome in adults.

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—*metabolic risk factors*—that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD).[1] Patients with the metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus. Another set of conditions, the *underlying risk factors*, give rise to the metabolic risk factors. In the past few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients who manifest the multiple components of the metabolic syndrome. These criteria have varied somewhat in specific elements, but in general they include a combination of both underlying and metabolic risk factors.

The most widely recognized of the metabolic risk factors are atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose. Individuals with these characteristics commonly manifest a prothrombotic state and a proinflammatory state as well. Atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apolipoprotein B (apoB), increased small LDL particles, and a reduced level of HDL cholesterol (HDL-C). The metabolic syndrome is often referred to as if it were a discrete entity with a single cause. Available data suggest that it truly is a syndrome, ie, a grouping of ASCVD risk factors, but one that probably has more than one cause. Regardless of cause, the syndrome identifies individuals at an elevated risk for ASCVD. The magnitude of the increased risk can vary according to which components of the syndrome are present plus the other, non–metabolic syndrome risk factors in a particular person.

Underlying Risk Factors and Metabolic Syndrome

The predominant underlying risk factors for the syndrome appear to be abdominal obesity[2–4] and insulin resistance[5,6]; other associated conditions can be physical inactivity,[3,7] aging,[8] and hormonal imbalance.[9] An atherogenic diet (eg, a diet rich in saturated fat and cholesterol) can enhance risk for developing cardiovascular disease in people with the syndrome, although this diet is not listed specifically as an underlying risk factor for the condition.[1] One theory holds that insulin resistance is the essential cause of the metabolic syndrome.[10] There is no doubt that insulin resistance predisposes to the hyperglycemia of type 2 diabetes mellitus. Multiple metabolic pathways have also been proposed to link insulin resistance and compensatory hyperinsulinemia to the other metabolic risk factors.[10,11] It is recognized that some people who are not obese by traditional measures nevertheless are insulin resistant and have abnormal levels of metabolic risk factors. Examples are seen in individuals with 2 diabetic parents or 1 parent and a first- or second-degree relative[12]; the same is true for many individuals of South Asian ethnicity.[13,14] Although insulin-resistant individuals need not be clinically obese, they nevertheless commonly have an abnormal fat distribution that is characterized by predominant upper body fat. Upper-body obesity correlates

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strongly with insulin resistance. Excess upper body fat can accumulate either intraperitoneally (visceral fat) or subcutaneously. Many investigators claim that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment[4,15–21]; other workers find that excess subcutaneous abdominal (or truncal) fat also carries a significant association with insulin resistance.[22–27] Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper-body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity.[28] An interesting feature of upper-body obesity is an unusually high release of nonesterified fatty acids from adipose tissue[12,14,28]; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver seemingly predisposes to insulin resistance[29] and dyslipidemia.[30]

According to many experts, the increasing burden of obesity in the United States is the driving force behind the rising prevalence of the metabolic syndrome.[1–4,31,32] This view needs to be harmonized with the insulin resistance hypothesis. Abnormalities in adipose tissue metabolism may be the crux of the issue. Adipose tissue in obese people is insulin resistant, which raises nonesterified fatty acid levels, worsening insulin resistance in muscle[29,33] and altering hepatic metabolism[31]; in addition, the adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance and/or modify risk for ASCVD.[34] These include increased production of inflammatory cytokines,[35,36] plasminogen activator inhibitor-1,[37] and other bioactive products[38–40]; at the same time the potentially protective adipokine, adiponectin, is reduced.[41,42] All of these changes have been implicated as causes of the metabolic risk factors. Indeed, as mentioned before, some individuals exhibit the metabolic syndrome with only a moderate degree of total body obesity.[43,44] Notable are many South Asians who appear to be inherently insulin resistant,[45] a condition that is exacerbated by mild abdominal obesity.[14] Moreover, the population of the United States varies considerably in degree of insulin resistance[46]; those having more inherent insulin resistance can develop the metabolic syndrome with only moderate excess in abdominal fat,[43,44] but even people with little or no inherent insulin resistance can develop the metabolic syndrome if they accumulate marked abdominal obesity.[3,8] These findings support the idea that body fat distribution, particularly excess abdominal fat, plays an important role in the etiology of the syndrome.

Recently, this syndrome has been noted to be associated with a state of chronic, low-grade inflammation.[47,48] Some researchers speculate that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both adipose tissue and muscle.[48–51] In the presence of obesity, adipose tissue indeed produces cytokines in excess, whereas output of adiponectin is diminished; these responses appear to heighten the connection between obesity and inflammation.[35] Interestingly, insulin-resistant people manifest evidence of low-grade inflammation even without an increase of total body fat.[52]

Finally, considerable individual and ethnic variation exists in the clinical pattern of metabolic risk factors in obese/insulin-resistant subjects.[53,54] It is likely that the expression of each metabolic risk factor falls partially under its own genetic control, which influences the response to different environmental exposures. For example, a variety of polymorphisms in genes affecting lipoprotein metabolism are associated with worsening of dyslipidemia in obese people.[55,56] Similarly, a genetic predisposition to defective insulin secretion when combined with insulin resistance can raise plasma glucose to abnormal levels.[57]

Although the metabolic syndrome unequivocally predisposes to type 2 diabetes mellitus,[48,58–62] many investigators of cardiovascular diseases consider this syndrome to be a multidimensional risk factor for ASCVD.[1,58] Several recent reports show that the metabolic syndrome is associated with greater risk for cardiovascular disease,[63–73] but once type 2 diabetes mellitus emerges, cardiovascular risk increases even more.[74] Finally, insulin resistance and the metabolic syndrome are associated with a variety of other conditions[75–77]; some of these are fatty liver,[30,78] polycystic ovary syndrome,[79] cholesterol gallstones,[80] sleep apnea,[81] lipodystrophies,[82] and protease-inhibitor therapy for HIV.[83] These associations are generating considerable interest in several other fields of medicine.

Metabolic Risk Factors, ASCVD, and Type 2 Diabetes Mellitus

The metabolic risk factors consist of those factors that seemingly have a direct effect on atherosclerotic disease. Among these, as stated earlier, *atherogenic dyslipidemia* consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apoB, increased small LDL particles, and a reduced level of HDL-C.[1] Among triglyceride-rich lipoproteins, remnant lipoproteins almost certainly are the most atherogenic.[1] Many studies further suggest that the smallest particles in the LDL fraction carry the greatest atherogenicity.[84] The atherogenic potential of lipoprotein remnants and small LDL could be confounded in part by their common association with an increased total number of apoB-containing lipoproteins in circulation; this increased number is reflected by an elevation of serum total apoB.[85–89] Finally, the lipoprotein field widely holds that low levels of HDL are independently atherogenic[1]; multiple mechanisms are implicated to explain this relationship.[90]

Other metabolic risk factors likewise appear individually to be atherogenic. Among these are *hypertension, elevated plasma glucose,* a *prothrombotic state,* and a *proinflammatory state.* Indeed, 3 of the metabolic risk factors—elevated apoB-containing lipoproteins,[1] low HDL-C levels,[1] and hypertension[91]—are well established, major risk factors. Each imparts increased risk even when only marginally abnormal, as often observed in the metabolic syndrome. A growing body of data additionally implicates high circulating levels of prothrombotic factors in the causation of ASCVD events, possibly by predisposing to thrombotic episodes.[92–94] Many reports also show that the presence of a proinflammatory state, as revealed by increased inflammatory markers,[95,96] denotes a higher risk for acute cardiovascular syndromes.

TABLE 1. Previous Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

Clinical Measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity* **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	None, **but any 3 of the following 5 features**	IGT or IFG **plus any of the following based on clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women†	BMI ≥25 kg/m^2	Increased WC (population specific) **plus any 2 of the following**
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)‡	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)
Other	Microalbuminuria			Other features of insulin resistance§	

T2DM indicates type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; and TG, triglycerides. All other abbreviations as in text.

*Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (eg, 94 to 102 cm [37 to 39 in]). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference.

‡The 2001 definition identified fasting plasma glucose of ≥110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥100 mg/dL (5.6 mmol/L), in accordance with the American Diabetes Association's updated definition of IFG.[46,47,77]

§Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

Finally, a variety of mechanisms to explain how elevated plasma glucose may promote atherosclerosis are postulated.[97] Regardless, once type 2 diabetes mellitus compounds the metabolic syndrome, risk for ASCVD events increases still more.

Clinical Diagnosis of Metabolic Syndrome

Many investigations confirm that multiple cardiovascular risk factors of endogenous origin commonly aggregate in one individual. Although this aggregation was originally observed many years ago,[98,99] more recently, several terms have been proposed to describe this clustering: metabolic syndrome,[100] syndrome X,[101] the "deadly quartet,"[102] insulin-resistance syndrome,[103,104] and hypertriglyceridemic waist.[105] The term *metabolic syndrome* is most commonly used in the cardiovascular field. Although the metabolic syndrome is often referred to as a discrete entity, it is important to recognize, as noted earlier, that it is a *syndrome* and not a defined uniform entity. No single pathogenesis has been elucidated, nor may one exist. Thus, the syndrome could range from a cluster of unrelated risk factors to a constellation of risk factors linked through a common underlying mechanism. From a clinical standpoint, presence of the metabolic syndrome identifies a person at increased risk for ASCVD and/or type 2 diabetes mellitus. Eventually, a better understanding of the specific cause(s) of the syndrome may provide an improved estimate of risk of developing ASCVD or type 2 diabetes mellitus for individuals. For now, however, the presence of the syndrome is a more general indicator of higher risk for these conditions. Because of a documented high relative risk for ASCVD events and type 2 diabetes mellitus, the metabolic syndrome undoubtedly carries a relatively high lifetime risk for these disorders even when shorter-term (10-year) risk is in the low-to-moderate range.[63–73]

In the effort to introduce the metabolic syndrome into clinical practice, several organizations have attempted to formulate simple criteria for its diagnosis (Table 1). The first proposal came in 1998 from a consultation group on the definition of diabetes for the World Health Organization (WHO).[106] This group emphasized insulin resistance as the major underlying risk factor and required evidence of insulin resistance for diagnosis. This followed on the widely held belief that insulin resistance is the primary cause of the syndrome. A diagnosis of the syndrome by WHO criteria could thus be made when a patient exhibited one of several markers of insulin resistance plus 2 additional risk factors. Although insulin resistance is difficult to measure directly in a clinical setting, several types of indirect evidence were accepted, ie, impaired glucose intolerance [IGT], impaired fasting glucose [IFG], type 2 diabetes mellitus, or impaired disposal of glucose under hyperinsulinemic, euglycemic conditions. The other risk factors used for diagnosis included obesity, hypertension, high triglycerides, reduced HDL-C level, or microalbuminuria. The consultation group suggested categorical cutpoints to define each of these factors. Importantly, the WHO group allowed the term *metabolic syndrome* to be used in patients with type 2 diabetes mellitus who otherwise met the requirements for the syndrome. They reasoned that patients with type 2 diabetes mellitus often have a clustering of ASCVD risk factors, which puts them at particularly high risk for ASCVD.[69,70]

In 1999, the European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition.[107] This group used the term *insulin resistance syndrome*

rather than metabolic syndrome. They likewise assumed that insulin resistance is the major cause and required evidence of it for diagnosis. By their criteria, plasma insulin levels in the upper quartile of the population defined insulin resistance. An elevated plasma insulin plus 2 other factors—abdominal obesity, hypertension, elevated triglycerides or reduced HDL-C, and elevated plasma glucose—constituted a diagnosis of the insulin-resistance syndrome. Notably, EGIR focused more on abdominal obesity than did WHO, but in contrast to WHO, EGIR excluded patients with type 2 diabetes mellitus from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced alternative clinical criteria for defining the metabolic syndrome.[1] In so doing, the purpose of ATP III was to identify people at higher long-term risk for ASCVD who deserved clinical lifestyle intervention to reduce risk. The ATP III criteria did not require demonstration of insulin resistance per se. It was noted that direct measures of insulin resistance are laborious and not well standardized. Moreover, less-specific measures, such as glucose tolerance tests, are not routinely used in clinical practice. Although the ATP III panel recognized the phenomenon of clustering of metabolic risk factors, it did not draw conclusions on mechanistic pathogenesis. The ATP III criteria thus required no single factor for diagnosis, but instead made the presence of 3 of 5 factors the basis for establishing the diagnosis; these were abdominal obesity (also highly correlated with insulin resistance), elevated triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting glucose (IFG or type 2 diabetes mellitus).

Although ATP III did not make any single risk factor (eg, abdominal obesity) a requirement for diagnosis, it nonetheless espoused the position that abdominal obesity is an important underlying risk factor for the syndrome. Its cutpoints for abdominal obesity came from the definition in the 1998 National Institutes of Health obesity clinical guidelines[108]; they were a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. These cutpoints identify approximately the upper quartile of the US population. Abdominal obesity at these cutpoints was not made a prerequisite for diagnosis because lesser degrees of abdominal girth often associate with other ATP III criteria. In fact, some individuals or ethnic groups (eg, Asians, especially South Asians) appear to be susceptible to development of the metabolic syndrome at waist circumferences below ATP III cutpoints. Thus, ATP III specifically noted that some individuals having only 2 other metabolic syndrome criteria appear to be insulin resistant even when the waist circumference is only marginally elevated, eg, 94 to 101 cm in men or 80 to 87 cm in women. If so, they should benefit from clinical intervention similarly to many others who have greater increases in waist circumference, ie, ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. ATP III, like WHO, allowed for a diagnosis of metabolic syndrome in the presence of type 2 diabetes because of the high risk for ASCVD among multiple-risk factor patients with diabetes. When type 2 diabetes mellitus is present, concomitant metabolic risk factors must not be overlooked because of strong evidence that intervention on them can substantially reduce risk for ASCVD.

In 2003, the American Association of Clinical Endocrinologists (AACE) modified ATP III criteria to refocus on insulin resistance as the primary cause of metabolic risk factors.[109] Like the EGIR,[107] they used the name *insulin resistance syndrome*. Major criteria were IGT, elevated triglycerides, reduced HDL-C, elevated blood pressure, and obesity. No specified number of factors qualified for diagnosis, which was left to clinical judgment. Other factors used to inform clinical judgment were a family history of ASCVD or type 2 diabetes mellitus, polycystic ovary syndrome, and hyperuricemia. By the AACE's definition, once a person develops type 2 diabetes mellitus, the term insulin resistance syndrome no longer applies.

In 2005, the International Diabetes Foundation (IDF) published new criteria that again modified the ATP III definition.[110] The IDF writing group included several members of the original WHO consultation group. They liked the ATP III definition because of its clinical simplicity. They furthermore considered that abdominal obesity is so highly correlated with insulin resistance that other, more laborious measures of insulin resistance are unnecessary. The IDF clinical definition thus makes the presence of abdominal obesity necessary for diagnosis. When such is present, 2 additional factors originally listed in the ATP III definition are sufficient for diagnosis. IDF recognized and emphasized ethnic differences in the correlation between abdominal obesity and other metabolic syndrome risk factors. For this reason, criteria of abdominal obesity were specified by nationality or ethnicity based on best available population estimates. For people of European origin (Europid), the IDF specified thresholds for abdominal obesity to be waist circumferences ≥94 cm in men and ≥80 cm in women. These thresholds apply to Europids living in the Americas as well as Europe. For Asian populations, except for Japan, thresholds were ≥90 cm in men and ≥80 cm in women; for Japanese they were ≥85 cm for men and ≥90 cm for women.

The present AHA/NHLBI statement, in contrast to IDF, maintains the ATP III criteria except for minor modifications (Table 2). This decision is based on the conclusion that ATP III criteria are simple to use in a clinical setting and have the advantage of avoiding emphasis on a single cause. No compelling reasons were found for making a change. In addition, a large number of studies have been carried out to evaluate the ATP III criteria for the metabolic syndrome.[35,111–133] The majority of these reports are supportive of the present structure of ATP III criteria. It must be noted in Table 2, however, that the threshold for IFG was reduced from 110 to 100 mg/dL; this adjustment corresponds to the recently modified American Diabetes Association (ADA) criteria for IFG.[134] Otherwise, the statement maintains that continuity with the original ATP III definition, which has been widely adopted in the United States and elsewhere, is appropriate in the absence of new evidence to the contrary.

Present diagnostic criteria thus accord with ATP III by defining abdominal obesity as a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. As noted in ATP III,[1] some people will manifest features of

TABLE 2. Criteria for Clinical Diagnosis of Metabolic Syndrome

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

*To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (eg, ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

insulin resistance and the metabolic syndrome with only moderate increases in waist circumference (ie, between 94 and 101 cm in men or 80 and 87 cm in women). Among the characteristics that may predispose to insulin resistance and metabolic syndrome in such individuals are the following: (1) type 2 diabetes mellitus in first-degree relatives before age 60 years,[109] (2) polycystic ovary disease,[9] (3) fatty liver,[135] (4) C-reactive protein (CRP) >3 mg/L (if measured),[96] (5) microalbuminuria (if detected),[136–141] (6) impaired glucose tolerance (if measured),[109] and (7) elevated total apoB (if measured).[88,89] In addition, some populations are predisposed to insulin resistance, metabolic syndrome, and type 2 diabetes mellitus, with only moderate increases in waist circumference (ie, populations from South Asia, China, Japan, and other Asian countries).[127,130,131,142] None of these phenotypic features or ethnic differences was included in the ATP III diagnostic criteria; but if individuals with such characteristics have only moderate elevations of waist circumference plus at least 2 ATP III metabolic syndrome features, then consideration should be given to managing them similarly to people with 3 ATP III risk factors.

The recent IDF definition of metabolic syndrome is similar in practice to the modified ATP III definition adopted in the present statement. Obvious differences are 2-fold: IDF requires abdominal obesity as 1 factor and sets lower thresholds for abdominal obesity than used in the United States. Even so, most subjects with waist circumference ≥94 cm in men or ≥80 cm in women plus 2 other risk factors (IDF definition) will in fact have 3 risk factors (ATP III definition). The defining third risk factor will be either a higher waist circumference (≥102 cm for men and ≥88 cm for women) or 1 other risk component. For this reason, in the United States, for the most part the same individuals will be identified by either definition. At the same time, when applying ATP III criteria in Asian countries, lower waist circumferences, as defined by IDF for these populations, appear to be appropriate as 1 risk factor.[127,130,131,142] The same waist criteria are reasonable for Asians living in the United States (Table 2).

Clinical Management of the Metabolic Syndrome

Goals of Clinical Management

The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for clinical atherosclerotic disease. Even in people with the metabolic syndrome, first-line therapy is directed toward the major risk factors: LDL-C above goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for ASCVD. The prime emphasis in management of the metabolic syndrome per se is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes. Effective lifestyle change will reduce all of the metabolic risk factors. Then, if absolute risk is high enough, consideration can be given to incorporating drug therapy to the regimen. The priority of drug therapy is elevations of LDL-C, blood pressure, and glucose; current guidelines for their management should be followed. Moreover, efforts should be made to bring about smoking cessation in any cigarette smokers.

Table 3 summarizes the current goals and recommendations for management of each of the risk factors of the metabolic syndrome. These recommendations are derived in large part from existing NHLBI, AHA, and ADA guidelines for management of specific risk factors. It is important to note that individuals who have established ASCVD and/or diabetes can still have the metabolic syndrome. The evidence bases for most of the recommendations have been presented in background documents for obesity,[108] physical inactivity,[143] lipids,[1] high blood pressure,[91] and diabetes.[134] The present

statement attempts to provide an integrated approach to the management of a multidimensional risk factor condition.

Risk Assessment

ASCVD

A series of studies[63–73] have found that many middle-aged people with the metabolic syndrome are at increased absolute risk for ASCVD in the near future (eg, 10-year risk). Moreover, as stated previously, because of the high relative risk for ASCVD, long-term (lifetime) risk for ASCVD is increased even when 10-year risk is not considered to be high, eg, in young adults who develop the syndrome. An exacerbating factor raising lifetime risk for ASCVD is an increased likelihood for developing premature type 2 diabetes mellitus.

To reduce lifetime risk for ASCVD, all individuals found to have the metabolic syndrome deserve long-term management and follow-up in the clinical setting. The primary aim is to reduce the underlying risk factors. Such individuals need to be categorized according to *absolute* 10-year risk.[1] Individuals with any clinical form of ASCVD or with diabetes belong in the *high-risk* category.[1] For metabolic syndrome patients without ASCVD or diabetes, Framingham risk scoring should be performed to estimate 10-year risk for coronary heart disease (CHD).[1] This assessment triages patients into 3 risk categories based on 10-year risk for CHD: *high risk* (10-year risk >20%), *moderately high risk* (10-year risk 10% to 20%), or *lower to moderate risk* (10-year risk <10%).

Thus, detecting metabolic syndrome is only one part of overall risk assessment for cardiovascular disease. The metabolic syndrome per se is not an adequate tool to estimate 10-year risk for CHD. Although patients with the metabolic syndrome are at higher lifetime risk, in the absence of diabetes they do not necessarily have a high 10-year risk. Estimating 10-year risk entails key risk factors beyond those of the syndrome, ie, age, sex, smoking, and total cholesterol. Moreover, risk factors of the metabolic syndrome are not graded for severity as are the risk factors contained in Framingham scoring. Framingham investigators find little or no increase in predictive power for CHD by adding abdominal obesity, triglycerides, or fasting glucose to their 10-year risk algorithm.[58,144] These factors come into play in the longer term. Whether adding still other factors—apoB, small LDL, CRP, and insulin levels—will enhance shorter-term prediction of ASCVD has not been rigorously tested in multivariable models.

Type 2 Diabetes Mellitus

In individuals with diabetes, the coexistence of other metabolic syndrome factors denotes a higher risk for future development of ASCVD.[69] Compared with other metabolic risk factors, IFG (fasting glucose 100 to 125 mg/dL) carries the greatest predictive power for diabetes.[112] A closely related measure is IGT, defined as a 2-hour plasma glucose ≥140 mg/dL and <200 mg/dL observed during a standard oral glucose tolerance test (OGTT). The ADA has introduced the term "prediabetes" to apply to individuals with either IFG or IGT.[134] Some investigators recommend OGTT for normoglycemic subjects who have the metabolic syndrome to detect IGT or occult diabetes. IGT in fact exceeds IFG in frequency; it consequently uncovers more individuals at increased risk for diabetes. In part to reduce the need for OGTT in routine practice, the ADA recently reduced the threshold for IFG to 100 mg/dL, from its previous 110 mg/dL.[134] People who have fasting glucose in the range of 100 to 110 mg/dL are now said to have IFG; many such people would have IGT if tested by OGTT. OGTT nonetheless remains an option in normoglycemic individuals who appear to be at elevated risk for developing diabetes. In fact, performing OGTT in people with IFG will identify some individuals who already have type 2 diabetes mellitus. Intensive lifestyle management of individuals with IFG (or IGT) will delay conversion to type 2 diabetes mellitus.[145]

Management of Underlying Risk Factors

Although many people may be genetically susceptible to the metabolic syndrome, rarely does it become clinically manifested in the absence of some degree of obesity and physical inactivity. Consequently, therapies to mitigate these underlying risk factors constitute first-line intervention. If cigarette smoking, another risk factor for ASCVD, is present, then it likewise deserves intensive cessation effort. The reason to modify underlying risk factors is to prevent or delay onset of ASCVD; and if type 2 diabetes mellitus is not already present, a concomitant goal is to prevent it as well.

Abdominal Obesity

Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome.[108,146] Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity and the use of principles of behavior change. The first aim of weight loss is to achieve a decline of about 7% to 10% from baseline total body weight during a period of 6 to 12 months. This will require decreasing caloric intake by 500 to 1000 calories per day. Greater physical activity helps to enhance caloric deficit. Achieving the recommended amount of weight loss will reduce the severity of most or all of the metabolic risk factors. Maintenance of a lower weight is just as important; this requires long-term follow-up and monitoring.[108]

Currently available weight-loss drugs possess limited utility in the management of obesity. Nevertheless, in some patients they may be helpful. Bariatric surgery is being used increasingly in the United States for severe obesity. Individuals at high risk for the complications of obesity may benefit. Weight-loss surgery is not without risk, however. Selection of patients must be made with a team of healthcare professionals who are qualified to make appropriate clinical judgments about the pros and cons of this approach.

Physical Inactivity

Increasing physical activity assists in weight reduction; it also has beneficial effects on metabolic risk factors; and importantly, it reduces overall ASCVD risk.[147] Current recommendations for the public call for accumulation of ≥30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all, days of the week[77,143]; even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people

TABLE 3. Therapeutic Goals and Recommendations for Clinical Management of Metabolic Syndrome

Therapeutic Target and Goals of Therapy	Therapeutic Recommendations
Lifestyle risk factors	Long-term prevention of CVD and prevention (or treatment) of type 2 diabetes mellitus
Abdominal obesity	
Reduce body weight by 7% to 10% during year 1 of therapy. Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI <25 kg/m^2)	Consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake, and formal behavior-modification programs when indicated to maintain/achieve waist circumference of <40 inches in men and <35 inches in women. Aim initially at slow reduction of ~7% to 10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity	
Regular moderate-intensity physical activity; at least 30 min of continuous or intermittent (and preferably ≥60 min) 5 d/wk, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or an exercise test, to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity: brisk walking, preferably daily, supplemented by increase in daily lifestyle activities (eg, pedometer step tracking, walking breaks at work, gardening, housework). Longer exercise times can be achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (eg, recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet	
Reduced intake of saturated fat, *trans* fat, cholesterol	Recommendations: saturated fat <7% of total calories; reduce *trans* fat; dietary cholesterol <200 mg/dL; total fat 25% to 35% of total calories. Most dietary fat should be unsaturated; simple sugars should be limited.
Metabolic risk factors	Shorter-term prevention of CVD or treatment of type 2 diabetes mellitus
Atherogenic dyslipidemia	
Primary target: elevated LDL-C (see Table 4 for details)	Elevated LDL-C (see Table 4 for details)
Secondary target: elevated non-HDL-C	Elevated non-HDL-C
High-risk patients*: <130 mg/dL (3.4 mmol/L) (optional: <100 mg/dL [2.6 mmol/L] for very high-risk patients†)	Follow strategy outlined in Table 4 to achieve goal for LDL-C First option to achieve non-HDL-C goal: Intensify LDL-lowering therapy Second option to achieve non-HDL-C goal: Add fibrate (preferably fenofibrate) or nicotinic acid if non-HDL-C remains relatively high after LDL-lowering drug therapy Give preference to adding fibrate or nicotinic acid in high-risk patients Give preference to avoiding addition of fibrate or nicotinic acid in moderately high-risk or moderate-risk patients All patients: If TG is ≥500 mg/dL, initiate fibrate or nicotinic acid (before LDL-lowering therapy; treat non-HDL-C to goal after TG-lowering therapy)
Moderately high-risk patients‡: <160 mg/dL (4.1 mmol/L) Therapeutic option: <130 mg/dL (3.4 mmol/L)	
Moderate-risk patients§: <160 mg/dL (4.1 mmol/L)	
Lower-risk patients‖: <190 mg/dL (4.9 mmol/L)	
Tertiary target: reduced HDL-C	Reduced HDL-C
No specific goal: Raise HDL-C to extent possible with standard therapies for atherogenic dyslipidemia	Maximize lifestyle therapies: weight reduction and increased physical activity Consider adding fibrate or nicotinic acid after LDL-C-lowering drug therapy as outlined for elevated non-HDL-C
Elevated BP	
Reduce BP to at least achieve BP of <140/90 mm Hg (or <130/80 mm Hg if diabetes present). Reduce BP further to extent possible through lifestyle changes.	For BP ≥120/80 mm Hg: Initiate or maintain lifestyle modification in all patients with metabolic syndrome: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products For BP ≥140/90 mm Hg (or ≥130/80 mm Hg for individuals with chronic kidney disease or diabetes): As tolerated, add BP medication as needed to achieve goal BP
Elevated glucose	
For IFG, delay progression to type 2 diabetes mellitus. For diabetes, hemoglobin A_{1c} <7.0%	For IFG, encourage weight reduction and increased physical activity. For type 2 diabetes mellitus, lifestyle therapy, and pharmacotherapy, if necessary, should be used to achieve near-normal HbA1C (<7%). Modify other risk factors and behaviors (eg, abdominal obesity, physical inactivity, elevated BP, lipid abnormalities).
Prothrombotic state	
Reduce thrombotic and fibrinolytic risk factors	High-risk patients: Initiate and continue low-dose aspirin therapy; in patients with ASCVD, consider clopidogrel if aspirin is contraindicated. Moderately high-risk patients: Consider low-dose aspirin prophylaxis
Proinflammatory state	Recommendations: no specific therapies beyond lifestyle therapies

TG indicates triglycerides; BP, blood pressure; CVD, cardiovascular disease; CHF, congestive heart failure; BMI, body mass index; IFG, impaired fasting glucose; and ASCVD, atherosclerotic cardiovascular disease.

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes TIA or stroke of carotid origin or >50% carotid stenosis.

†Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease + any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and metabolic syndrome.

‡Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%. Factors that favor therapeutic option of non-HDL-C <100 mg/dL are those that can raise individuals to upper range of moderately high risk: multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).

§Moderate-risk patients are those with 2+ major risk factors and 10-year risk <10%.

‖Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.

with the metabolic syndrome. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day, will promote weight loss or weight-loss maintenance. Preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities.[77] The latter include multiple short (10- to 15-minute) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (eg, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training[148]; avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. Self-monitoring of physical activity can help to achieve adherence to an activity program.

Current AHA guidelines[143] call for clinical assessment of risk for future ASCVD events before initiating a new exercise regimen. This includes a detailed history of physical activity. For high-risk patients (eg, those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under medical supervision. AHA guidelines[143] further recommend exercise testing before vigorous exercise in selected patients with cardiovascular disease and other patients with symptoms or those at high risk. It is not necessary, however, that all individuals beginning an exercise program of moderate intensity that is moderately progressive undergo an exercise stress test, although this issue remains controversial.

Atherogenic and Diabetogenic Diets

Beyond weight control and reduction of total calories, the diet should be low in saturated fats, *trans* fats, cholesterol, sodium, and simple sugars.[1,149] In addition, there should be ample intakes of fruits, vegetables, and whole grains; fish intake should be encouraged with recognition of concerns about the mercury content of some fish (see the Food and Drug Administration web site, www.cfsan.fda.gov/~dms/admehg3.html).[91,150,151] Very high carbohydrate intakes can exacerbate the dyslipidemia of the metabolic syndrome. ATP III[1] recommended that for individuals entering cholesterol management the diet should contain 25% to 35% of calories as total fat. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C. On the other hand, if the fat content falls below 25%, triglycerides can rise and HDL-C levels can decline[152]; thus, very-low-fat diets may exacerbate atherogenic dyslipidemia. To avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome, some investigators favor fat intakes in the range of 30% to 35%; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in the range of 25% to 30%.

There has long been an interest in the question of whether changing the macronutrient content of the diet can promote weight reduction. For many years, a low-fat diet was advocated because the high caloric density of fat could increase the likelihood of obesity. More recently, interest has grown in the possibility that high-protein, low-carbohydrate diets will enhance weight reduction.[153] The rationale seems to be that fat and protein offer satiety that is absent with carbohydrates. That this effect of fat and protein on satiety makes the diet more effective for producing weight loss is a disputable hypothesis. Moreover, research documenting that high-fat/high-protein/low-calorie diets can achieve long-term maintenance of a lower body weight is lacking. In fact, after 1 year of consumption of low-carbohydrate diets, severely obese patients show no more weight reduction than those eating a conventional weight-loss diet.[154] High-fat diets not only tend to be higher in saturated fat but they often are deficient in fruits, vegetables, and whole grains—all of which are important components in currently recommended diets. High-protein diets of any sort are not well tolerated by individuals with chronic renal disease who have markedly reduced glomerular filtration rate; excess protein enhances phosphorus load, which can cause acidosis and worsen insulin resistance.[155,156] Finally, preoccupation with macronutrient composition to promote weight loss fails to identify the key factors affecting body weight. Effective weight loss requires a combination of caloric restriction, physical activity, and motivation; effective lifelong maintenance of weight loss essentially requires a balance between caloric intake and physical activity.

Management of Metabolic Risk Factors

Beyond lifestyle therapies directed toward underlying risk factors, attention must be given to the metabolic risk factors. If ASCVD or diabetes is present, or if the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for risk factors may be required as defined by current guidelines.[1,91,134] Recommended principles of management for each of the metabolic risk factors are also considered in Table 3.

Atherogenic Dyslipidemia

As noted before, this condition consists of abnormal levels of triglycerides and apoB, small LDL particles, and low HDL-C. According to ATP III,[1] atherogenic dyslipidemia can become a target for lipid-lowering therapy *after* the goal for LDL-C has been attained. In other words, as long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other lipid risk factors are secondary. The LDL-C goals depend on estimates of absolute risk. Table 4 reviews LDL-C goals that are consistent with recommendations of ATP III[1] and its recent update.[157] In patients with atherogenic dyslipidemia in whom serum triglyceride levels are ≥200 mg/dL, non-HDL-C becomes the next target of treatment after the LDL-C goal is reached (Table 3). A related and potential secondary target is an elevated total apoB[158]; this measure denotes the number of atherogenic lipoproteins in circulation.[85–89] Some investigators hold that total apoB is superior to non-HDL-C as a target of lipid-lowering therapy.[89,159,160] ATP III nonetheless identified non-HDL-C rather than total apoB as a secondary target (after LDL-C) because accurate measurement of non-HDL-C is more readily available in clinical practice. Goals for non-HDL-C parallel those for LDL-C except that the former are 30 mg/dL higher (Table 3).

When triglycerides are ≥500 mg/dL, triglyceride-lowering drugs should be considered to prevent the development of acute pancreatitis.[1] To achieve non-HDL-C goals at triglyc-

TABLE 4. Elevated LDL-C: Primary Target of Lipid-Lowering Therapy in People at Risk for ASCVD

Goals of Therapy	Therapeutic Recommendations
High-risk patients*: <100 mg/dL (2.6 mmol/L) (for very high-risk patients‡ in this category, optional goal <70 mg/dL)	High-risk patients: lifestyle therapies† plus LDL-C-lowering drug to achieve recommended goal If baseline LDL-C ≥100 mg/dL, initiate LDL-lowering drug therapy If on-treatment LDL-C ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination) If baseline LDL-C <100 mg/dL, initiate LDL-lowering therapy based on clinical judgment (ie, assessment that patient is at very high risk)
Moderately high-risk patients§: <130 mg/dL (3.4 mmol/L) (for higher-risk patients‖ in this category, optional goal is <100 mg/dL (2.6 mmol/L)	Moderately high-risk patients: lifestyle therapies+LDL-lowering drug if necessary to achieve recommended goal when LDL-C ≥130 mg/dL (3.4 mmol/L) after lifestyle therapies If baseline LDL-C is 100 to 129 mg/dL, LDL-lowering therapy can be introduced if patient's risk is assessed to be in upper ranges of this risk category
Moderate-risk patients¶: <130 mg/dL (3.4 mmol/L)	Moderate risk patients: lifestyle therapies+LDL-C lowering drug if necessary to achieve recommended goal when LDL-C ≥160 mg/dL (4.1 mmol/L) after lifestyle therapies
Lower-risk patients#: <160 mg/dL (4.9 mmol/L)	Lower-risk patients: lifestyle therapies+LDL-C lowering drug if necessary to achieve recommended goal when LDL-C ≥190 mg/dL after lifestyle therapies (for LDL-C 160 to 189 mg/dL, LDL-lowering drug is optional)

*High-risk patients are those with established ASCVD, diabetes, or 10-year risk for coronary heart disease >20%. For cerebrovascular disease, high-risk condition includes transient ischemic attack or stroke of carotid origin or >50% carotid stenosis.

†Lifestyle therapies include weight reduction, increased physical activity, and antiatherogenic diet (see Table 3 for details).

‡Very high-risk patients are those who are likely to have major CVD events in next few years, and diagnosis depends on clinical assessment. Factors that may confer very high risk include recent acute coronary syndromes, and established coronary heart disease+any of following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), and multiple risk factors of metabolic syndrome.

§Moderately high-risk patients are those with 10-year risk for coronary heart disease 10% to 20%.

‖Factors that can raise individuals to upper range of moderately high risk are multiple major risk factors, severe and poorly controlled risk factors (especially continued cigarette smoking), metabolic syndrome, and documented advanced subclinical atherosclerotic disease (eg, coronary calcium or carotid intimal-medial thickness >75th percentile for age and sex).

¶Moderate-risk patients are those with 2+ major risk factors and 10-year risk <10%.

#Lower-risk patients are those with 0 or 1 major risk factor and 10-year risk <10%.

erides <500 mg/dL, triglyceride-lowering drugs may be useful in combination with LDL-lowering therapy. Beyond lowering of non-HDL-C, a tertiary aim in patients with atherogenic dyslipidemia is to raise HDL-C when it is reduced. No specific goal of therapy is recommended for low HDL-C, but HDL-C should be raised to the extent possible after attaining goals for LDL-C and non-HDL-C.

If non-HDL-C remains elevated after the LDL-C goal is reached (Table 4), at least 2 therapeutic options are available. First, intensification of LDL lowering often also reduces non-HDL-C. For example, statins lower both LDL-C and non-HDL-C by a similar percentage; moreover, statins reduce risk for ASCVD events in patients with the metabolic syndrome.[161] Second, a triglyceride-lowering drug can be added to LDL-lowering therapy. Both fibrates and nicotinic acid reduce non-HDL-C and reportedly decrease risk for ASCVD in patients with the metabolic syndrome/type 2 diabetes mellitus.[162–164] For this reason, combining a fibrate or nicotinic acid with LDL-C-lowering treatment becomes an option.[165,166] Both fibrates and nicotinic acid raise HDL-C as well as reduce triglycerides and small LDL particles. If a statin is being used for LDL-C lowering, fenofibrate seems preferable to gemfibrozil because risk for severe myopathy appears to be lower for fenofibrate in combination with statins.[167] One recent report,[168] however, failed to find a difference in myopathy risk between gemfibrozil and fenofibrate when either was used in combination with statins (other than cerivastatin, which is no longer available). Patients with IFG, IGT, or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening of hyperglycemia.[169] Lower doses of nicotinic acid lessen this risk. Whether adding a fibrate or nicotinic acid to statin therapy will reduce cardiovascular events more than a statin alone has not been evaluated adequately in randomized clinical trials; consequently the use of this combination probably should be limited largely to high-risk individuals who stand to gain the most from it. If a fibrate or nicotinic acid is used with a statin, higher doses of the statin generally should be avoided to minimize risks for myopathy or hepatic effects.

Elevated Blood Pressure

When overt hypertension is present without diabetes or chronic kidney disease, the goal for antihypertensive therapy is a blood pressure of <140/90 mm Hg.[91] In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg.[91] Beyond these specific treatment goals, lifestyle changes deserve increased emphasis in people with the metabolic syndrome; the goals here are to reduce blood pressure as much as possible even in the absence of overt hypertension and to obtain other metabolic benefits of lifestyle change. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies: weight control, increased physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits and vegetables and low-fat dairy products, in accord with the Dietary Approaches to Stop Hypertension (DASH) diet.[91] If hypertension cannot be adequately controlled by lifestyle

therapies, antihypertensive drugs usually are necessary to prevent long-term adverse effects, eg, myocardial infarction, stroke, and chronic kidney disease.[91] The benefits of therapy extend to patients with type 2 diabetes mellitus whose blood pressure is above goal level, and presumably to hypertensive patients with the metabolic syndrome. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present.[170] Indeed, inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) may lower risk for diabetes itself.[171] ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have left ventricular dysfunction.[172] Debate persists about the latter strategy. The results of a large clinical trial[173] raised the possibility that use of diuretics in patients with IFG or IGT may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events.[91,173] Most investigators in the hypertension field believe that the potential benefit of low-dose diuretics in combination antihypertensive therapy outweighs their risk.

Elevated Fasting Glucose

In the metabolic syndrome diagnosis, elevated fasting glucose (≥100 mg/dL) includes both IFG and type 2 diabetes mellitus. In metabolic syndrome patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of type 2 diabetes mellitus.[145,174] In addition, metformin,[145] thiazolidinediones,[175,176] and acarbose[177] will lower risk for type 2 diabetes mellitus in people with IFG or IGT. Except for a preliminary trial with acarbose,[178] no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risk for cardiovascular events. Moreover, neither metformin nor thiazolidinediones are recommended in this statement solely for the purpose of preventing diabetes because their cost-effectiveness and long-term safety have not been documented.

For patients with established type 2 diabetes mellitus, clinical trials confirm a reduction in cardiovascular risk from treatment of dyslipidemia[161–163,179–181] and hypertension.[91] Glycemic control to a hemoglobin A_{1c} of <7% reduces microvascular complications and may decrease risk for macrovascular disease as well.[182]

Prothrombotic State

People with the metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. These abnormalities, however, are not routinely detected in clinical practice. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established ASCVD provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. In metabolic syndrome patients who are at moderately high risk for ASCVD events, aspirin prophylaxis is an attractive therapeutic option to lower vascular events.[183]

TABLE 5. Additional Measures Reported to Be Associated With Metabolic Syndrome and in Need of More Research

Abnormal body fat distribution
General body fat distribution (dual-energy x-ray absorptiometry [DXA])
Central fat distribution (CT/MRI)
Adipose tissue biomarkers: leptin, adiponectin
Liver fat content (magnetic resonance spectroscopy)
Myocellular fat (magnetic resonance spectroscopy)
Atherogenic dyslipidemia (beyond elevated triglyceride and non-HDL-C and low HDL)
Apolipoprotein B
Small LDL particles
Triglycerides/HDL-C ratios
Dysglycemia
Fasting glucose
OGTT
Insulin resistance (other than elevated fasting glucose)
Fasting insulin/proinsulin levels
Homeostasis model assessment for insulin resistance (HOMA-IR)
Insulin resistance by Bergman Minimal Model
Elevated free fatty acids (fasting and during OGTT)
Vascular dysregulation (beyond elevated blood pressure)
Measurement of endothelial dysfunction
Microalbuminura
Chronic renal disease
Proinflammatory state
Elevated high-sensitivity CRP
Elevated inflammatory cytokines (eg, interleukin-6)
Low levels of adiponectin
Prothrombotic state
Fibrinolytic factors (plasminogen activator inhibitor-1, etc)
Clotting factors (fibrinogen, etc)
Hormonal factors
Corticosteroid axis
Polycystic ovary syndrome

Proinflammatory State

People with the metabolic syndrome frequently have a proinflammatory state as shown by elevated cytokines (eg, tumor necrosis factor-α and interleukin-6) and acute-phase reactants (eg, CRP, fibrinogen).[96,184] Measurement of CRP is the simplest way to identify a proinflammatory state in clinical practice. CRP levels >3 mg/L can be taken to define such a state in a person without other detectable causes.[95] If CRP is measured, the finding of an elevated level supports the need for lifestyle changes. The latter, particularly weight reduction, will reduce CRP levels and presumably will mitigate the underlying inflammatory stimulus.[185] No drugs that act exclusively through this mechanism are available for reducing cardiovascular risk. However, several drugs used to

treat other metabolic risk factors have been reported to reduce CRP levels (eg, statins, nicotinic acid, fibrates, ACE inhibitors, thiazolidinediones).[186–188] At present, these drugs cannot be recommended specifically to reduce a proinflammatory state independent of their indications for other risk factors.

Future Research

This statement recognizes several issues related to the metabolic syndrome that require additional research for clarification. Foremost is the need for improved strategies to achieve and sustain long-term weight reduction and increased physical activity. Moreover, a lack of understanding of the genetic and metabolic contributions to the causation of the syndrome stands in the way of developing new therapeutic approaches. The need exists, therefore, for additional basic and clinical research designed to better understand pathophysiology from the standpoint of genetics, molecular biology, and cellular signaling. At present, tools to assess short-term risk for ASCVD and diabetes in patients with the metabolic syndrome need significant improvement. Although statins and other LDL-lowering drugs effectively reduce the risk for ASCVD, adequate therapies for remaining dyslipidemias either are not available or have not yet been proved to reduce risk in combination with LDL-lowering drugs. Insulin resistance is an attractive target for prevention of ASCVD; clinical trials to date, however, have not been carried out to confirm ASCVD risk reduction from decreasing insulin resistance per se. The emerging relationship between a proinflammatory state and the development of both ASCVD and diabetes deserves much additional investigation. Finally, the cost-effectiveness of various drugs, both alone and in combination therapies, requires more extensive evaluation.

The metabolic syndrome can be clinically manifested in a variety of ways. A sizable number of metabolic changes thus occur in people with clinical evidence of the syndrome. Identification of these changes should provide a broader picture of the metabolic status of an affected individual. They may also give insights into pathogenesis. At present, many of these factors cannot be readily identified in routine clinical practice. Nevertheless, several factors appear to overlap with alternative measures of the same underlying or metabolic risk factor. For example, there are several ways to estimate body fat distribution. In addition, multiple tests for insulin resistance have been proposed; each examines a different aspect of the insulin-resistance phenomenon. The IDF report lists many of these factors as important targets for research even when they are not used for routine clinical diagnosis. Table 5 presents a list of research targets similar to those proposed by the IDF. Epidemiological, metabolic, and genetic studies directed to a broad profile of parameters related to the metabolic syndrome should provide new insights into the responsible pathways. It is not expected that these measures will be used in routine clinical practice because the incremental value of measurement is uncertain. Their study at present is expected to be mainly for research, ie, metabolic and epidemiological studies.

Conclusions

In summary, the following points should be emphasized:

1. The metabolic syndrome is a term for a constellation of endogenous risk factors that increase the risk of developing both ASCVD and type 2 diabetes mellitus.
2. The syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups.
3. In the United States, the syndrome is strongly associated with the presence of abdominal obesity.
4. The metabolic syndrome is a secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary targets for risk reduction.
5. Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome. If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated.
6. To date, there is insufficient evidence for primary use of drugs that target the underlying causes of the metabolic syndrome.
7. Considerable additional research is needed to better refine the most appropriate therapies for individuals with the metabolic syndrome.

TABLE 6. Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers Bureau/ Honoraria	Ownership Interest	Consultant/Advisory Board	Other
James I. Cleeman	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Fernando Costa	American Heart Association	None	None	None	None	None	None
Stephen R. Daniels	Cincinnati Children's Hospital Medical Center	Pfizer, Astra-Zeneca, Inamed	None	None	None	Abbott Laboratories	None
Karen A. Donato	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Robert H. Eckel	University of Colorado Health Sciences Center	None	None	None	None	None	None
Barry A. Franklin	William Beaumont Hospital	None	None	Pfizer	None	None	None
David Gordon	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Scott M. Grundy	University of Texas Southwestern Medical Center	Abbott, GlaxoSmithKline, Merck, KOS	Department of Veterans Affairs, Reynolds, National Institutes of Health	None	None	Pfizer, Sanofi, Abbott Laboratories	None
Ronald M. Krauss	Children's Hospital Oakland Research Institute	None	None	Abbott, Merck	None	Abbott, AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer	None
Peter J. Savage	National Heart, Lung, and Blood Institute	None	None	None	None	None	None
Sidney C. Smith, Jr.	University of North Carolina Medical School	None	None	None	Johnson & Johnson, Medtronic, Intuitive Surgery	None	None
John A. Spertus	Saint Luke's Hospital of Kansas City	CV Therapeutics	National Heart, Lung, and Blood Institute	None	CV Outcomes, Outcomes Instruments, Inc	CV Therapeutics	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

TABLE 7. Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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John Brunzell	University of Washington	None	None	None	None	None	None
Harold Franch	Emory University; Atlanta VA Medical Center	National Institutes of Health; Department of Veterans Affairs	AHA Kidney Foundation	None	None	None	None
Daniel Porte, Jr.	Independent consultant	None	None	None	Abbott Laboratories; Amcyte; Diamedica Inc; Merck	Amcyte; Amylin; Aventis; Bristol-Myers Squibb; Diamedica Inc; Johnson & Johnson; Kowa Research Institute; Mankind Corporation; Novartis; Sanyko; Sanofi-Synthelabo; Sanofi Aventis; Sanwa Kaguku Kenkyusho; Takeda	None
Paul Thompson	Hartford Hospital	Otsuka; Merck; Pfizer; AstraZeneca; Schering-Plough; KOS	None	Merck; Pfizer; Schering-Plough; AstraZeneca	Pfizer; Schering-Plough; Zoll; Merck	Merck; Pfizer; Schering-Plough; AstraZeneca; Bristol-Myers Squibb; Reliant; KOS; Sanyko	None

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